Bandolier 146

Independent evidence-based thinking about health care

On observation

Readers will have to dig hard to find many systematic reviews or randomised trials in this issue. We concentrate instead on good observational studies. Observational studies are great for raising questions, but not for answering them, or as some clever folk once put it "observational studies propose, RCTs dispose" [1]. Observational studies can, however, get you into the papers if written with sufficient extrapolation, and fed to journalists gullible to the hyperbole of press releases.

Yet when good they can help us think. This time we think about anaemia, especially anaemia in older people, and of chronic disease. Bandolier has visited this before, but more and better information tells us how big the problem is, in human and monetary terms. No RCTs provide answers about treatment, at least not just yet, though extrapolation from other clinical areas shows that treating anaemia is a good thing. It is certainly expensive, even when treating US economic information for transatlantic inflation.

Learning from observations of others is how we progress, especially when they are systematic and detailed. So it is with cat-scratch disease in older people, where presentation can be quite different in older people than in children.

Sticking to the point

Some topics are important but difficult. Bandolier is frustrated that more clear evidence is not available concerning adherence, compliance, concordance, persistence, or whatever. There is little but a quick canter through some recent studies, but they shed only a little light. Most important is perhaps that presentation methods change patient perception of adverse events, and in an RCT too!

Reference:

1 G Davey Smith, S Ebrahim. Data dredging, bias, or confounding. They can all get you into the BMJ and the Friday papers. BMJ 2002 325: 1437-1438.

In this issue

Anaemia and mortality in older people

Bandolier 137 examined the increasing prevalence of anaemia with age six in larger studies, using WHO criteria for anaemia of a haemoglobin of less than 120 g/L for women and less than 130 g/L for men. Anaemia has many causes in older people. The question remains about the consequences. A large cohort study [1] indicates that anaemia may be independently associated with increased mortality.

Study

This was a prospective observational study of risk factors for, and consequences of, cardiovascular disease in older adults in the community. Beginning in about 1990, it recruited people aged 65 years or older in four communities in the USA. Exclusion criteria were being wheelchair bound, treatment for cancer, or living in an institution. At enrolment there was a physical examination and history, together with various tests.

Deaths were identified from databases, and by bi-annual follow up, up to mid-2001. Analysis was by quintile of haemoglobin level (performed separately for men and women), and by use of the WHO criteria for anaemia.

Results

Baseline haemoglobin measurements were available of 5,800 participants, average age 74 years at baseline, with a median follow up of 11.2 years, and 54,000 person years of follow up. Using WHO criteria, 498 were anaemic initially, a prevalence of 8.5%. Anaemia was commoner in black participants (18%) than white (7.0%), but similar in men and women.

Participants in the lowest quintile of haemoglobin were older, more likely to be black, and had more comorbid conditions. The strongest correlates were with low BMI, low activity levels, fair or poor self reported health, frailty, heart failure, stroke, or transient ischaemic attack. Low haemoglobin was also associated with higher creatinine levels, CRP, and fibrinogen, and lower serum albumin and white cell count.

Low haemoglobin was associated with higher mortality (Figure 1), whether using the WHO criteria, or the lowest quintile. Death rates over the 11 years were 57% for those with WHO-defined anaemia but 39% for those without anaemia, with high levels of statistical significance, and for both cardiovascular and non-cardiovascular causes of death.

Figure 1: Mortality in older people with WHO criteria of anaemia, and by quintile of Hb

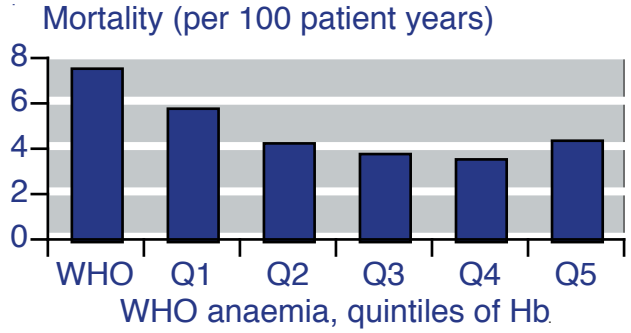


Table 1: Statistical comparisons

Group	Hazard ratio (95% CI)
WHO criteria	1.4 (1.2 to 1.6)
Lowest Hb quintile Q1	1.3 (1.2 to 1.5)
Q2	1.2 (0.99 to 1.3)
Q3	1.0 (0.9 to 1.2)
Q4	1.0
Highest Hb quintile Q5	1.2 (1.01 to 1.4)

Hazard ratios using adjustment for age, sex, race, and baseline characteristics

Compared with the fourth quintile (women with haemoglobin levels of 139 to 144 g/L and men with levels of 151 to 156 g/L), significant increases in mortality were seen for both the lowest and the highest quintiles of haemoglobin, using adjustments for a wide range of possibly confounding characteristics (Table 1).

Comment

The prevalence of anaemia was 8.5%, within the prevalence range seen previously in larger studies (Bandolier 137). This study clearly associates lower haemoglobin levels with increased mortality in a reasonably large population over a long time. The association with higher mortality was particularly strong using the WHO criteria for anaemia for women and men. There may be increased mortality at higher levels of haemoglobin, but that was much less strong. Other studies have found similar association between anaemia and higher mortality in older people, and in specific conditions. This paper is a rich source of references.

There is much we do not know, of course. We do not know the cause of anaemia in these people, and no observational study can determine causality. We can speculate that long-term anaemia can contribute to adverse physiological changes. We can only guess at the moment whether treating the anaemia would be beneficial in older people, though it is in specific conditions.

Reference:

1 NA Zakai et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. Archives of Internal Medicine 2005 165: 2214-2220.

Anaemia and rheumatoid arthritis

Anaemia is known to be common in rheumatoid arthritis, deriving both from long term use of NSAIDs and anaemia of chronic disease often associated with infection, inflammation, or malignancy. How common anaemia is in rheumatoid arthritis has been investigated by a systematic review [1], which also sought evidence about the effects of treating the anaemia.

Systematic review

Good searching strategies were continued to February 2003. Outcomes of interest were prevalence of anaemia, as well as the impact of anaemia on a range of clinical and functional outcomes, and quality of life.

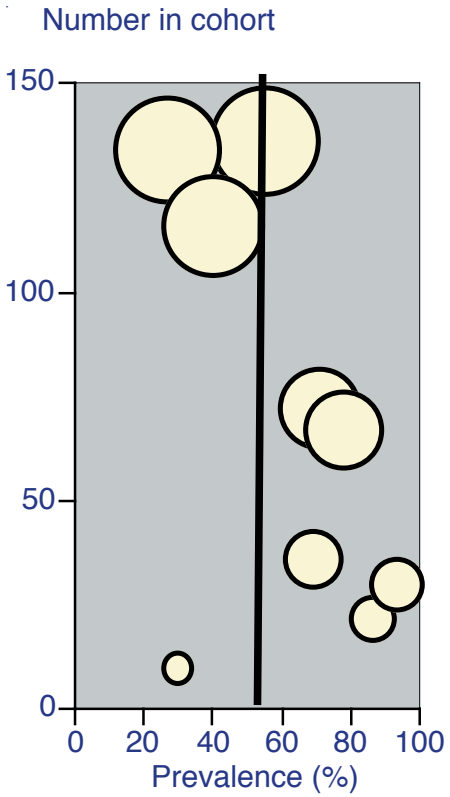
Results

In all 19 studies were included, all of them relatively small.

Prevalence

Ten studies with 623 adult patients with rheumatoid arthritis and 213 with juvenile arthritis reported on prevalence, using different criteria for anaemia. Some reported anaemia in total, some by severity, and some by sex. In the nine studies with adult patients with rheumatoid arthritis, prevalence ranged from 30% to 93%, with an overall prevalence of 54% (Figure 1). In juvenile arthritis it was 41%. There was insufficient information for sensible further breakdown of the figures.

Figure 1: Prevalence of investigator diagnosed anaemia in individual cohorts of patients with rheumatoid arthritis



Outcomes

Only small numbers of small studies reported outcomes associated with anaemia. Based on the information available, anaemia has little apparent impact on morning stiffness, swollen joints, Ritchie index, or pain. There may be improvements in muscle strength if anaemia is corrected, based on tiny numbers.

However, increasing haemoglobin levels in patients with rheumatoid arthritis and anaemia is probably beneficial in other ways. Three studies all suggested good improvements in energy levels, and another three studies indicated positive changes in quality of life measures.

Comment

This is a surprisingly small amount of evidence given that rheumatoid arthritis is not uncommon, that considerable efforts have gone into improving treatments, that anaemia is acknowledged to be a problem in the condition, and that it is seen by some as a model for the anaemia of chronic diseases.

Reference:

1 A Wilson et al. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. American Journal of Medicine 2004 116 (7A): 50S-70S.

Economic burden of anaemia

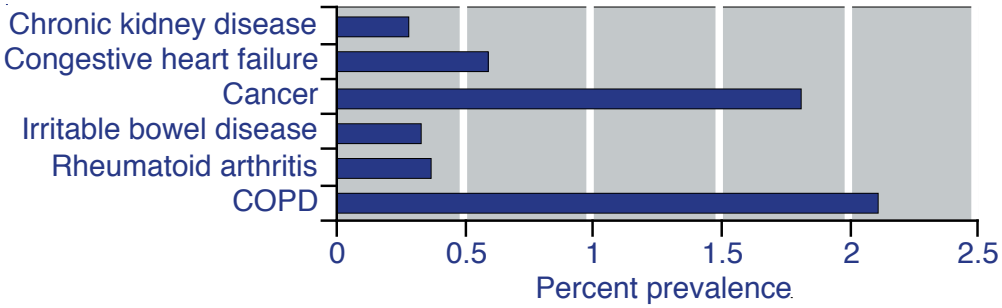
Anaemia is common in chronic diseases, and in the elderly. It is associated with more severe disease, and with increased mortality. It should follow that it is also expensive. Just how expensive it is is investigated in two reports of a study of an insured population of workers from the USA [1,2].

Study

The basis of the analyses is from retrospective claims data from commercial and Medicare plans, covering over two million employees. The population was selected from only those plans with complete capture of costs, including prescription medicines.

Anaemia was identified from diagnostic, procedure, or drug codes, but excluding acute anaemia. Six specific conditions with known high rates of anaemia were also evaluated, chronic kidney disease, cancer, congestive heart failure, irritable bowel disease, and rheumatoid arthritis, with COPD in the second but not first analysis.

Figure 1: Prevalence of six conditions in an insured population



Results

First analysis [1]

During 2000 there were 2.3 million plan members with continuous coverage. In this period there were 81,000 cases coded for anaemia, a prevalence of 3.5%. Using 2.2 million plan members with at least one year of continuous coverage over the years 1999 to 2001, 118,000 patients with a coding of anaemia were matched with 36,000 patients without a coding for anaemia, all of whom made claims during an average of nine months of follow up.

Despite 87% of the anaemic patients having no anaemia-specific treatment (transfusion, erythro-

Figure 2: Prevalence of anaemia in the six conditions

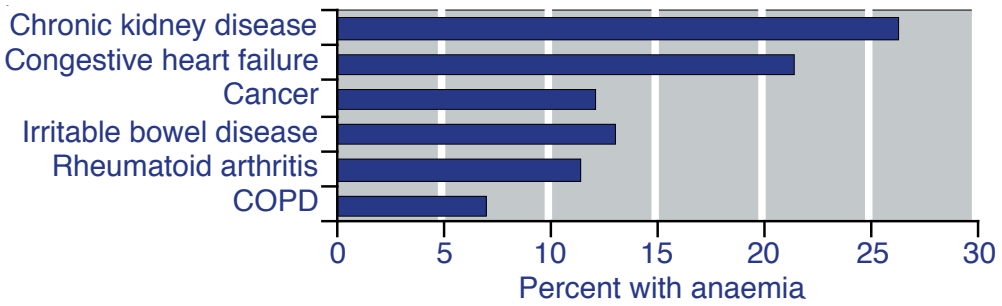
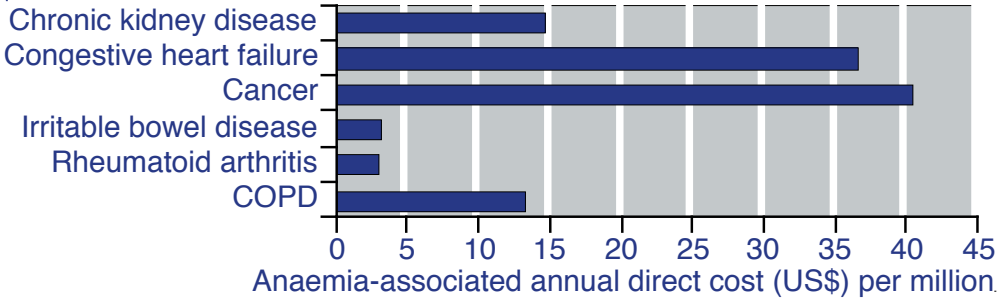


Figure 3: Anaemia-associated annual costs per million population



poietin, B12 or iron injections), there were significantly more outpatient visits and inpatient days, laboratory tests and emergency room visits for anaemic patients. There were, for instance, one more day in hospital, one more outpatient visit, and three more laboratory tests per patient associated with anaemia. On average, payments per anaemic patient were $14,500, and for non-anaemic patients $9,500.

Second analysis [2]

Other analyses used about 2.2 million plan members with at least one year of continuous coverage over the years 1999 to 2001. Of these, 123,000 had at least one of the six study conditions (5.5% of the total study population), 14,400 (0.64% of the total population) also having anaemia. In the six conditions, average age ranged from 46 years for irritable bowel disease to 53 years for cancer.

The prevalence of the conditions in this population is shown in Figure 1, and the prevalence of anaemia in the specific conditions is shown in Figure 2.

For these six diseases, the direct costs of care were calculated for patients with and without anaemia, using modelling to take account of the probability of those with anaemia having more severe disease, and incurring greater costs because of that. Adjusting for severity halved the anaemia-associated direct costs.

Figure 3 shows the adjusted annual anaemia-associated direct costs modelled for one million people like those in the population studied. They were greatest for cancer and congestive heart failure, but combined for these six conditions, the total annual anaemia-associated cost was $110 million.

Comment

In terms of the population reported in these studies, most were between 30 and 70 years, and there were somewhat more women than men. The older old were not included because the bulk of the information was coming from an employed population. One person in about 20 had at least one of the six conditions, and 1 in about 160 also had anaemia. Those with anaemia cost more to treat over one year than those without anaemia, even after making allowances for the greater disease severity that accompanies anaemia.

For a hypothetical one million people like this, the burden of anaemia in these conditions was $110 million. In UK terms, with 28 million people in employment, a current exchange rate of $1.75 per £, and making an assumption that costs here are half those in the USA, one would not get much change out of £1 billion. That is more than in the Bandolier piggy bank, and makes independent thinking harder about anaemia sensible, rather than sponsored economic analysis.

References:
1 AR Nissenson et al. Economic burden of anemia in an insured population. Journal of Managed Care Pharmacy 2005 11: 565-574.
2 WB Ershler et al. Economic burden of patients with anemia in selected diseases. Value in Health 2005 8: 629-638.

Adherence update

Concordance, compliance, adherence, or persistence (readers can choose whichever most soothes their prejudices) is so important that Bandolier keeps a weather eye open for anything of interest or importance. The default condition is to find nothing either interesting or important, but just recently a few have swum into our ken that are interesting, and may be important. A quick canter through them, then.

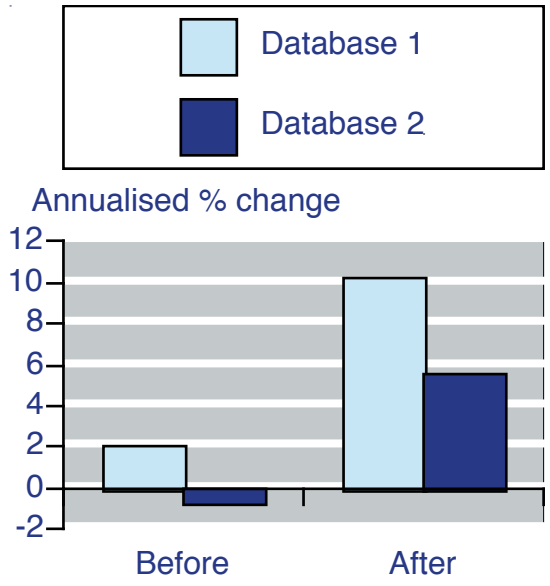
Physician adherence to guidelines

Improving treatment for hypertension is a good thing. In Canada a hypertension education programme began in 1999, with annual updates for evidence-based hypertension management recommendations, with an extensive implementation programme to enhance guideline uptake. A new report [1] examined two databases in Ontario to see what changes the programme had made.

The first database was for all treated hypertensives in a register of cardiovascular drug dispensing between 1998 and 2003. The second was for all treated elderly hypertensives without diabetes between 1994 and 2002. Results, in terms of annualised percentage change in prescribing of all antihypertensive drugs, are shown in Figure 1. In both databases, modest changes in prescribing before the introduction of the guideline and education programme were replaced by large increases in prescribing of antihypertensive drugs. Prescribing changes by class were consistent with programme guidance.

A second study [2] described a randomised study of 36 physicians and nurse practitioners, where an individualised intervention with advice concerning the individual patient, together with general guidance was compared with general guidance alone. The study covered about 4,500 patients, with an average age of 65 years.

Figure 1: Annualised percentage changes in total hypertensive medicine prescribing in two databases before and after the introduction of the Canadian guideline and education programme in 1999



In the study there was a greater increase in the proportion of patients whose prescribing was guideline concordant with individualised advice (11%) than with general guidance alone (4%). The proportion of patients with adequate blood pressure control increased from 39% to 47% with individualised guidance, and from 43% to 45% with general guidance alone. Overall, though, blood pressure changes (a 2 to 3 mmHg fall for systolic and diastolic) were the same for each group.

Money talks

We know that patient adherence to therapy is low, and the oft-quoted figure is that half of prescribed medicines are not taken. It is not always clear the extent to which any co-payments make a difference, but a new US study [3] suggests that co-payment can be an important factor.

The study was conducted in prescription management databases in Colorado and Nevada, with about 270,000 members, for six classes of drugs (calcium channel blockers, statins, oral contraceptives, inhaled corticosteroids, angiotensin receptor blockers and ACE inhibitors). The number of prescribed days covered was calculated for each class, and switching of drugs analysed, depending on whether the drug was generic (co-payment $5-$20), preferred brand name ($15-$40), or non-preferred brand name ($30-$60). The study followed 7,500 new prescriptions over one year (90% in middle or high income homes).

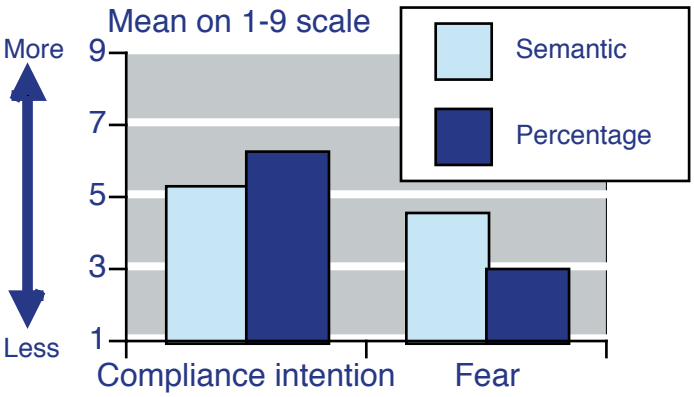
Over the year in these drug classes, the proportion of days covered was 56%. Results for individual classes are in Figure 2. The proportion of days covered was greatest for generics (59%) than preferred (57%) or non-preferred (52%). There were also fewer switches for generics (14%) than for preferred (20%) and non-preferred drugs (28%).

Adverse events talk too

Interviewing patients who are non-adherent demonstrates that adverse events are a major concern to patients. A Dutch study [4] examined 232 chronic prescriptions for long-term medicines. Almost half (46%) were not refilled over three months, and about a quarter of these patients did not refill their prescriptions because of adverse events.

Talking to patients about adverse events can help [5], but it may well depend on how the adverse event rates are described. A randomised trial in 120 subjects given information about medicine adverse events found they were more likely to be compliant, and had less fear (Figure 3), when presented with information about adverse events in percentage terms than in words (some people may experience….). Given information in words, the overestimation of risk to themselves was almost 10-fold.

Figure 3: Influence of presentation of adverse event description on compliance intention and fear of adverse events



Comment

This is a hugely important, though complicated, area. Many different aspects combine to influence professional and patient behaviour. While there is considerable evidence about the scale of the problem, there is considerably less about how to change things for the better. Bandolier will keep looking.

References:

1 NR Campbell et al. The impact of the Canadian Hypertension Education Program on antihypertension prescribing trends. Hypertension 2006 47: 22-28.

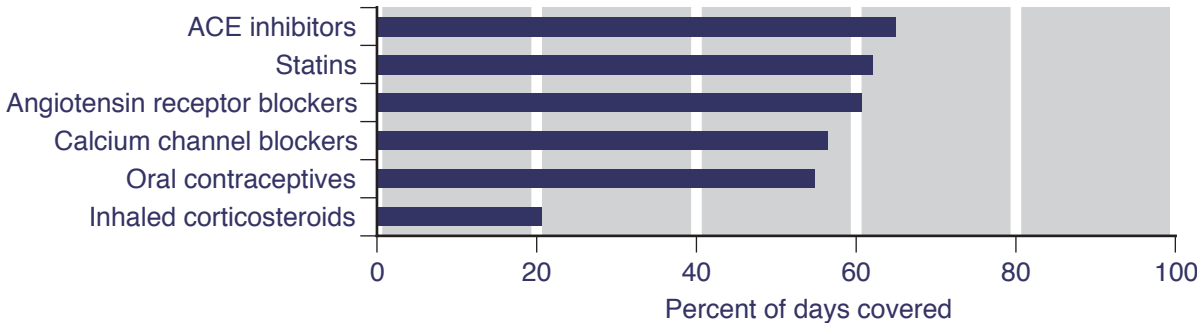
2 MK Goldstein et al. Improving adherence to guidelines for hypertension drug prescribing: cluster randomised controlled trial of general versus patient-specific recommendations. American Journal of Managed Care 2005 11: 677-685.

3 WH Shrank et al. The implications of choice. Prescribed generic or preferred pharmaceuticals improves medication adherence for chronic conditions. Archives of Internal Medicine 2006 166: 332-337.

4 JC Hugtenburg et al. Initial phase of chronic medication use; patients' reasons for discontinuation. British Journal of Clinical Pharmacology 2005 61: 352-354.

5 SD Young, DM Oppenheimer. Different methods of presenting risk information and their influence on medication compliance intentions: results of three studies. Clinical Therapeutics 2006 28: 129-139.

Figure 2: Average number of days covered by prescriptions in six drug classes



Cat scratch disease update

Cat-scratch disease has never been foremost in Bandolier's thoughts. For one thing it is relatively uncommon, is usually seen in children, and has a relatively straightforward diagnosis and treatment. There are a few hostages to fortune there, but that's the way it is oftentimes. Cat-scratch disease in older people wasn't even on the radar, but reports from a new study from Israel suggests that it has a different presentation than in younger people [1,2].

Study

This was a surveillance study began in Israel in 1991, and involved clinicians sending specimens from patients suspected to have cat-scratch disease to a single laboratory. If they met case definition criteria, they were enrolled into the study and demographic and clinical data collected prospectively with a structured questionnaire, supplemented by medical records if necessary.

A case was defined as at least one positive test, including PCR, antibodies, or culture, with a compatible clinical syndrome. Typical disease was defined as regional lymph node involvement without ocular, cutaneous, or visceral problems. Atypical included one of several problems, including ocular, encephalitis, endocarditis, fever of unknown origin, erythema nodosum, hepatitis, splenitis, or osteomyelitis.

Results

The group of 846 patients with confirmed cat-scratch disease formed the cohort. Typical disease was present in 85%. Overwhelmingly patients were young, with 80% of cases in under 40s, and 70% in under 30s. The average age was 18 years, with the highest number of cases between four and 14 years, and a smaller peak between 22 and 28 years (Figure 1, for age to 50 years).

Cat scratch disease was diagnosed in 52 patients at least 60 years or older [1]. Their presentation was different (Table 1). There were generally more women, but fewer with lymph node involvement. More of the older patients had atypical presentation, fever of unknown origin, encephalitis, and especially endocarditis. Diagnosis took longer in the over 60s, and fewer received antibiotics.

A second report of the same study [2] identified 24 patients with arthropathy, not usually associated with cat scratch disease. These patients were aged between 23 and 54 years, and were more likely (5/24; 21%) to have erythema nodosum than in patients without arthropathy (2%).

Table 1: Presentation in older patients

Feature	Percent with feature		Odds ratio (95% CI)
	<60 years (N=794)	≥60 years (N=52)	
Lymph node involved	94	77	0.2 (0.1 to 0.4)
General malaise	51	71	2.3 (1.2 to 4.3)
Female sex	41	58	2.0 (1.1 to 3.5)
Atypical presentation	14	33	3.1 (1.7 to 5.7)
Fever unknown origin	1.1	7.7	7.3 (2.2 to 25)
Encephalitis	0.6	3.8	6.3 (1.2 to 33)
Endocarditis	0.3	14	62 (12 to 300)

These patients with arthropathy had frequent involvement of knee, wrist, or ankle. All had regional lymph node involvement, and in 22/24 arthropathy developed within a week of appearance of lymph node involvement.

Average duration of arthropathy was 13 weeks, but that encompassed the enormous range of one to 240 weeks. Nineteen (74%) recovered, and in these recovery came within 24 weeks (median six weeks). In the other five patients the disease became chronic, persisting for 16-53 months at the latest follow up.

Comment

It is comforting that we can continue to learn using good quality observation. Diagnosing cat scratch disease in older people may be made easier by the increasing availability of genetic methods like PCR, especially of tissue for the causative agent, bartonella henselae. An interesting, though not extensive, study of patients with lymph node involvement [3] tells us that PCR is 100% specific – meaning that a negative test is a rule out. Using PCR, and the starting point of superficial lymph node involvement in one isolated area, the paper has what looks to be a useful, if untested, diagnostic algorithm.

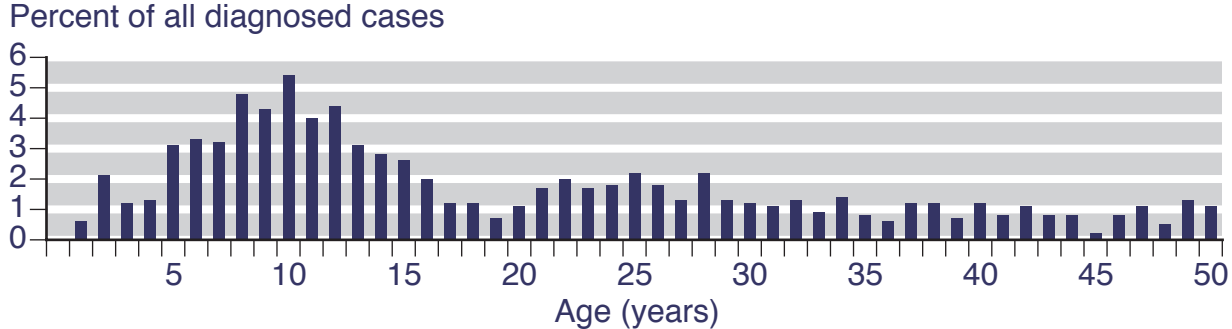
References:

1 R Bewn-Ami et al. Cat-scratch disease in elderly patients. Clinical Infectious Diseases 2005 41: 969-974.

2 M Giladi et al. Cat-scratch disease – associated arthropathy. Arthritis & Rheumatism 2005 52: 3611-3617.

3 Y Hansmann et al. Diagnosis of cat scratch disease with detection of *bartonella henselae* by PCR: a study of patients with lymph node involvement. Journal of Clinical Microbiology 2005 43: 3800-3806.

Figure 1: Age distribution of presenting cases, up to age 50 years



MINDSTRETCHER:
MAKING DECISIONS FOR GUIDELINES

This short piece is by way of being a reminder that making decisions about evidence is not always easy. You are going to be presented with some evidence about an important topic, drawn from a Cochrane review. You will have to choose how you word this in your guidelines.

Choices

There are three choices (A, B, or C) for a medicine that can reduce the likelihood of a serious, potentially fatal, event. Randomised trials have been conducted on identical patient groups, over roughly the same period of time, and using the same outcome.

Results

The results are shown in Table 1, and in Figures 1-3.

- Medicine A has the smallest number of patients, but a low NNT.
- Medicine B has more patients, and though the NNT is higher than the other two treatments, the proportion of patients with a bad event is lower, at 10%, than the other two treatments.
- Medicine C has the largest number of patients, four times more than medicine A, with equivalent results.

What do you use to choose? Here are some thoughts.

Medicine A had too few patients to be sure of the result. The problem with B is that while it produced the best result in terms of the lowest number of events, the rate with placebo was also low, yielding higher (worse) relative risk and NNT. Is the low rate with intervention a reflection of a different population (probably not), chance (probably not), or some other, unknown, feature of these particular studies (though some studies with other treatments had this characteristic; look at Figure 3)? Is medicine C the only safe choice?

Exposure

These data are for total endoscopic ulcers in trials lasting 3-12 months, from a Cochrane review updated in 2004 [1]. The treatments were:

A – High dose H2A (equivalent to at least 300 mg ranitidine twice daily)
B – Low dose H2A (equivalent to 150 mg ranitidine twice daily)
C - PPI

Comment

Most guidelines suggest using PPI or high dose H2A. To do so, they do not rely on these placebo-controlled studies alone. Nor should they, because the amount of information is limited, and these are, after all, at best surrogate measures for much more complicated events.

This is a case where a single direct comparison can really help. For instance, a large study compared omeprazole 20 mg daily with ranitidine 150 mg twice daily in 425 patients, and found omeprazole much superior (6% endoscopic ulcers, compared with 21% with ranitidine). For high dose H2A we do not even have that luxury, other than a comparison of two doses of nizatidine, with just eight events.

Yet the advice to use double dose histamine antagonists seems to be almost universal. It is curious that so much can be made of so little.

Reference:
1 A Rostrom et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database of Systematic Reviews, issue 1, 2006.

Figures 1-3: Individual trial results with (from left) A, B, and C

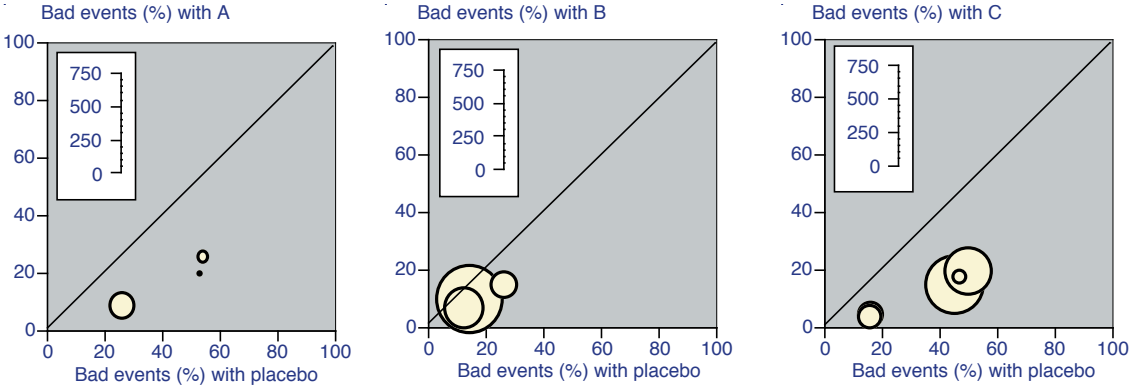


Table 1: Results for meta-analyses of trials of A, B, and C

Intervention	Number of Trials	Number of Patients	Percent bad events with Intervention	Percent bad events with Placebo	Relative risk (95% CI)	NNT (95% CI)
A	3	298	15	36	0.4 (0.3 to 0.6)	4.6 (3.2 to 8.4)
B	3	981	10	15	0.6 (0.4 to 0.9)	18 (10 to 65)
C	5	1216	15	36	0.4 (0.3 to 0.5)	4.7 (3.8 to 6.2)

Prognostic index for mortality

Knowing the future is impossible. Predicting what is likely to happen based on what we know already is tricky, but possible. A newly-developed prognostic index produces estimates of future four-year mortality in older adults based on age, illness, and function [1].

Study

Community dwelling adults older than 50 years provided information, mainly through telephone interviews. After exclusion of some with incomplete data, the final sample was 19,710 people across the United States. The study began in 1992, and expanded in 1998 to become a representative sample of the older US population. The sample was split into a developmental cohort and a validation cohort, based on geography.

A large amount of information was collected in the interview. As well as age, 18 behavioural and comorbidity variables were examined, including BMI, visual or hearing impairment, and self-reported illnesses. Participants were also asked about 21 functional measures, including activities like bathing, walking several city blocks, or pushing or pulling heavy objects.

Death was assessed using follow up procedures involving cross-referencing with US national death registers. Mortality over four years was then correlated with all the variables, with clever statistical methods to provide a model with 12 predictor variables. These were given points (Table 1), and the predictive accuracy of the developmental cohort was checked against the validation cohort.

Results

The mean age of participants was 67 years; 57% were women, and 10% black in the development cohort, and in the validation cohort mean age was 67 years, 56% were women, and 19% black. Over four years 12% and 13% of people in the cohorts died (over 2,400 deaths in total), and there were 68,000 person years of observation.

Figure 1: Mortality with development (square) and validation (circle) cohorts

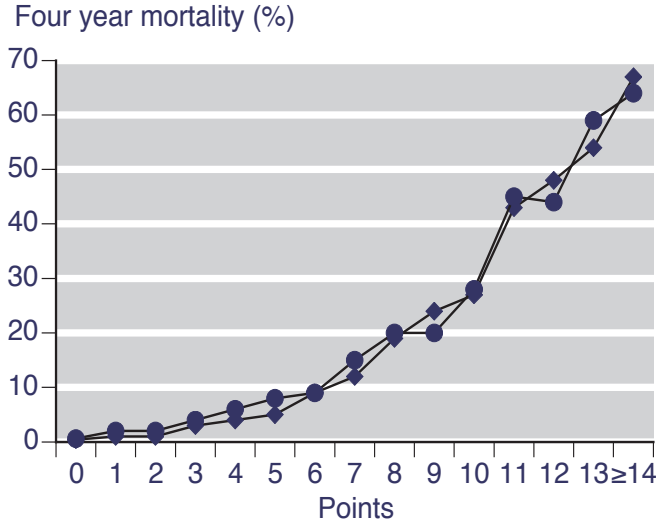


Table 1: Points and features in the index

	Risk factor	Points
Age	60-64	1
	65-69	2
	70-74	3
	75-79	4
	80-84	5
	>85	7
Male		2
Diabetes		1
Cancer		2
Lung disease		2
Heart failure		2
BMI<25		1
Current smoker		2
Problems		
bathing		2
managing finances		2
walking several blocks		2
pushing/pulling heavy objects		1

Risk stratification by points is shown in Figure 1, with increasing four-year mortality with increasing points in both development and validation cohort. Low risk (0-5 points) had a four year mortality of 3%, Medium risk (6-9 points) 15%, high risk (10-13 points) 41%, and for the highest risk of over 14 points it was 65%.

Comment

It is unusual to find a prognostic tool developed in such a large number of people over such a long period of time, and done so well. The paper comes with an example of a one-page questionnaire with 12 questions, which would allow a professional or patient to calculate their own score.

It is potentially useful, but where, and what for, remains to be seen.

Reference:

1 SJ Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006 295: 801-808.

EDITORS

Andrew Moore Henry McQuay
Pain Relief Unit
The Churchill, Oxford OX3 7LJ
Editorial office: 01865 226132
Editorial fax: 01865 226978
Email: andrew.moore@pru.ox.ac.uk
Internet: www.ebandolier.com
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